18. (New) The method of claim 1 or 5 wherein the human is a 5 to 14 year old.

19. (New) The method of claim 1 or 5 wherein the human is an adult.

20. (New) The method of claim 12 wherein the human is a 2 to 3 year old.

21. (New) The method of claim 12 wherein the human is a 4 to 5 year old.

22. (New) The method of claim 12 wherein the human is a 5 to 14 year old.

23. (New) The method of claim 12 wherein the human is an adult.

REMARKS

The claims

Claims 1-15 are currently pending. Claims 6-11 and 15 were withdrawn from consideration as a result of Applicant's election of Group 1, claims 1-5 and 12-14 in Paper No. 12. However, upon further review of elected claims 1-5 and 12-14, Applicant believes that claim 15 (which has been cancelled herein) should have been part of Group I, since claim 15 as filed concerned *S. typhi* Vi polysaccharide-rEPA conjugates linked by the ADH linker, as did elected claims 2 and 13 of Group I.

Claims 2, 6-11, 13 and 15 have been canceled herein without prejudice to new claims 16-23 have been added. Therefore, after entry of this amendment, claims 1, 3-5, 12, 14 and 16-23 will be pending.

Claims 1, 12 and 14 have been amended herein to indicate that the *S. typhi* Vi polysaccharide is derived from *S. typhi*. Support for this amendment can be found, e.g., on page 12, lines 19-24 of the specification, which describes the source of the *S. typhi* Vi

polysaccharide. Claims 1, 12 and 14 have also been amended to state that the *S. typhi* Vi polysaccharide is bound to the recombinant exoprotein A by an adipic acid dihydrazide linker (Note: this conjugate is called Vi- rEPA$_{II}$ herein). Support for this amendment can be found, e.g., on page 13, line 26 to page 14, line 20 of the specification. Claims 3 and 5 have been amended to correct dependency, due to the cancellation of claim 2.

New claims 16-19 are dependent on claims 1 and 5 and claims 20-23 are dependent on claim 12. New claims 16 and 20 recite that the human is a 2 to 3 year old and new claims 17 and 21 recite that the human is a 4 to 5 year old. Support for immunizing 2 to 3 year olds and 4 to 5 year olds with Vi-rEPA$_{II}$ is found, e.g., in Table II on page 36 of the specification. New claims 18 and 22 recite that the human is a 5 to 14 year old. Support for immunizing 5 to 14 year olds with Vi-rEPA$_{II}$ is found, e.g., on page 26, lines 18-26 of the specification. New claims 19 and 23 recite that the human is an adult. Support for immunizing adults with Vi-rEPA$_{II}$ is found, e.g., on page 19, lines 6-14 and in Table 4 of the specification.

Applicants expressly retain the right to pursue the subject matter of the originally filed claims which have been cancelled or amended herein in a continuation or other related application.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." Applicants respectfully submit that the above-mentioned amendments do not constitute new mater and respectfully request entry thereof.

Double Patenting

Claim 14 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39 and 44 of U.S. Patent No. 5,738,855. The examiner states that

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the now claimed Vi antigen may be obtained from any source as long as it is characterized as S.typhi Vi antigen, and the allowed claims recite a species of Vi antigen that is synthetic, or immunologically equivalent obtained from a plant or fruit. A genus claim is obvious over a species.

Office Action, 4/30/02, p. 2.

In response, Applicants note that claim 39 of U.S. 5,738,855 is directed to "An immunogen against *Salmonella typhi* comprising: a plant, fruit or synthetic saccharide modified by O-acetylation covalently linked to a carrier, said modified saccharide-carrier conjugate elicits antibodies in mammals, said antibodies are specifically immunoreactive against Vi of *Salmonella typhi*" and claim 44 of U.S. 5,738,855 is directed to "The immunogen of claim 39 wherein the carrier is selected from the group consisting of bacterial protein, viral protein, tetanus toxoid, diphtheria toxin, *Pseudomonas aeruginosa* exotoxin, *Ps. aeruginosa* toxoid, pertussis toxin, pertussis toxoid, *Clostridium perfringens* exotoxin, *Clostridium perfringens* toxoid, hepatitis B surface antigen, hepatitis B core antigen and Pseudomonas exoprotein A". Claim 14 of the involved application as amended herein is directed to "A vaccine composition comprising an immunologically effective amount of a molecular conjugate of *S. typhi* Vi polysaccharide derived from S. typhi covalently bound through an adipic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A, in a pharmaceutically acceptable carrier."

In view of the above amendment, Applicants respectfully submit that the rejection of claim 14 on the grounds of obviousness-type double patenting has been overcome and Applicants respectfully submit that the rejection of claim 14 on these grounds be reconsidered and withdrawn.

Claim Rejections - 35 U.S.C. § 102

Rejection of Claims 1-2, 5 and 12-under 35 U.S.C. 102(a)

Claims 1-2, 5 and 12-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Szu et al (December 8, 1997, different inventive entity).

35 U.S.C. 102(a) provides that

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The Examiner states that

> The claimed invention is directed to a composition comprising a S.typhi Vi polysaccharide covalently linked to Pseudomonas aeruginosa recombinant exoprotein A through a carboxylic acid dihydrazide linker and a method of inducing an immune response in a human and a method of vaccinating a human against S.typhi, both methods comprising the step of administering the composition to a human.
>
> (Composition) Szu et al disclose a composition comprising a S.typhi Vi polysaccharide covalently linked to Pseudomonas aeruginosa recombinant exoprotein a through a carboxylic acid dihydrazide linker, wherein the linker is identified by the abbreviation ADH.
>
> (Method) Szu et al also disclose a method of inducing an immune response in a human and a method of vaccinating a human against S.typhi, both methods comprising

> the step of administering the composition to a human, wherein the humans were children of 2-4 years old (see paragraphs 1-2).
>
> Inherently the reference anticipates the now claimed invention.
>
> Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.
>
> Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (Fed. Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art ... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Office Action, 4/30/02, pp. 3-4.

In response, Applicants first note that claims 2 and 13 have been cancelled herein, thereby rendering rejection of those claims on these grounds moot. Next, Applicants respectfully submit that the Szu et al. December 8, 1997 abstract is not prior art under 35 USC 102(a). Applicants point out that the Szu et al. 1997 abstract was co-authored by four of the five present inventors, *i.e.*, Drs. Szu, Kossaczka, Shiloach and Robbins. Dr. Schneerson, who was not listed as an author on the paper, participated in every aspect of the study described in the paper and in the involved application, i.e., in the discussions of how to form a conjugate vaccine using Vi polysaccharide, in the decision to use rEPA as the carrier, in writing the protocols for the clinical study, in developing the ELISA for assay of human serum antibodies and in the vaccination and monitoring at the site.

In *Ex parte Magner, Long, Ellis, and Grinstead*, 133 USPQ 404 (BdPatApp&Int 1961), three of four applicants for a patent were co-authors of a publication

published less than one year prior to the filing date. According to the Board, a declaration explaining the authorship of the publication and the inventorship of the application was sufficient to remove the reference:

> "The sole issue in this case is the procedure necessary for removing as a reference ... a publication by three of the four inventors of this application, published less than a year before the application filing date.
>
> ...
>
> The article is by three of the four joint inventors; we see no necessity for an affidavit under Rule 131 as no question of priority is involved. The question is as to attribution of inventorship--an explanation of the relation of the publication by three of the joint inventors to the application of all four of them. We think that the affidavit satisfies this requirement."
>
> *Ex parte Magner*, 133 USPQ 404, 404-405 (1961)

See also Ex parte Pavilanis, Marois, Boudreault, and Gilker, 166 USPQ 413 (BdPatApp&Int 1970). Applicants therefore submit herewith a declaration concerning coauthorship pursuant to 37 CFR §1.132, signed by all of the Applicants,[1] wherein they declare that Dr. Schneerson is named as a co-inventor because she participated in every aspect of the study as described above and wherein they also declare that the additional co-authors of the Szu et al. 1997 abstract are not inventors of the present application. In view of the declaration submitted herewith, the work described in the Szu et al. 1997 abstract is not "invented by another" and Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(a) over the Szu et al. 1997 abstract.

Furthermore, Applicants respectfully point out that the present inventors clearly had completed the experiments that are described in the Szu et al. 1997 abstract prior to its publication date, Applicants could submit a declaration under Rule 131 if required by the Examiner.

Applicants respectfully submit that in view of the accompanying declaration concerning coauthorship and remarks, the rejection of the claims under 35 U.S.C. §102(a) in view of the Szu et al. 1997 abstract be reconsidered and withdrawn.

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[1] Note: Three originals of this declaration are being submitted herewith, one signed by Drs. Szu, Robbins and Schneerson, one signed by Dr. Kossaczka and one signed by Dr. Shiloach.

Rejection of Claims 1-5 and 12-14 under 35 U.S.C. 102(e)

Claims 1-5 and 12-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Szu et al (October 17, 1994), i.e., U.S. Patent No. 5,738,855 issued April 14, 1998.

35 U.S.C. 102(e) provides that

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The examiner states that

> The claimed invention is directed to a composition comprising a S.typhi Vi polysaccharide covalently linked to Pseudomonas aeruginosa recombinant exoprotein a through a carboxylic acid dihydrazide linker and a method of inducing an immune response in a human and a method of vaccinating a human against S.typhi, both methods comprising the step of administering the composition to a human.

The examiner further states that

> (Composition) Szu et al [U.S. Patent No. 5,738,855] disclose a composition comprising a polysaccharide that has the equivalent immunoreactivity as that of S.typhi Vi polysaccharide antigen obtained from a different source, but antibodies stimulated to the polysaccharide specifically immunoreact with S.typhi Vi polysaccharide (see Table 2, col. 14, line 45; claims 40 and 49). The Vi same/equivalent antigen was covalently linked to Pseudomonas aeruginosa recombinant exoprotein a (see claim 44) through a carboxylic acid dihydrazide linker (see claim 14), wherein the linker is identified by the abbreviation ADH.

The examiner further states that

> (Method) Szu et al [U.S. Patent No. 5,738,855] also disclose a method of inducing an immune response in a human and a method of vaccinating a human against S.typhi, both methods comprising the step of administering the composition to a human, wherein the humans received a dose of about 25 micrograms (see col. 15, Example 7 and claim 49).
>
> Inherently the reference anticipates the now claimed invention.
>
> Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.
>
> Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (Fed. Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art ... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Office Action, 4/30/02, pp. 3-4.

In response, Applicants first note that claims 2 and 13 have been cancelled herein, thereby rendering rejection of those claims on these grounds moot. Applicants next note that anticipation of an invention is established under 35 USC §102 "when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention. RCA Corp. v. Applied Digital Data Sys., Inc., 730 F.2d 1440, 1444 (Fed. Cir.), cert dismissed, 468 US 1228 (1984) (citing Kalman v. Kimberly Clark Corp., 718 F.2d 760, 762 (Fed. Cir. 1983). For a reference to be anticipatory, it must clearly and

unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference. In re Arkley, 455 F.2d 586, 587-88 (CCPA 1972). The courts have repeatedly held that "shotgun disclosures" do not constitute evidence of anticipation or obviousness. See, e.g., In re Luvisi and Nohejl, 342 F.2d 102, 144 U.S.P.Q. 646, 650 (CCPA 1965), note 2:

> Our approach to this question [whether an expression which includes numerous species *ipso facto* discloses each and every one of those species] is to ask whether or not it can fairly and reasonably be said that one of ordinary skill in this art through a reading of the *entire* reference has constructive possession *the thing itself*, as opposed to possession of mere *language* which *embraces* the name of that thing. (Emphasis in original)

See also Ex parte Strobel and Catino, 160 U.S.P.Q 352 (Bd. Pat. App. & Int. 1968):

> We are of the view that the shotgun type disclosure of the reference ... would not guide one skilled in the art to choose appellants' restricted class of compounds from among the host of possible combinations and permutations suggested by patentees so as to make such class obvious within the meaning of 35 U.S.C. 103.

Claims 1, 12 and 14 have been amended herein to recite that the *S. typhi* Vi polysaccharide is derived from *S. typhi* and that the Vi polysaccharide is linked to recombinant exoprotein A by an adipic acid dihydrazide linker. Specifically, claims 1 and 3-5 are directed to methods of inducing serum antibodies in humans which protect against *S. typhi* infection in humans, wherein the *S. typhi* Vi polysaccharide is covalently bound to *r*EPA by means of an adipic acid dihydrazide linker (i.e., Vi-*r*EPA$_{II}$). Claim 12 is directed to a method for vaccinating a human against *S. typhi* infection, comprising administering to the human an immunizing amount of a composition comprising a molecular conjugate of *S. typhi*

Vi polysaccharide covalently bound through an adipic acid dihydrazide linker to rEPA (i.e., Vi-*r*EPA$_{II}$) in a pharmaceutically acceptable carrier. Claim 14 is directed to a vaccine composition comprising an immunologically effective amount of a molecular conjugate of *S. typhi* Vi polysaccharide covalently bound through an adipic acid dihydrazide linker to rEPA (i.e., Vi-*r*EPA$_{II}$), in a pharmaceutically acceptable carrier.

Table 2 of Szu et al U.S. 5,738,855 describes Vi-rEPA linked with SPDP, not ADH. (*See* Szu et al U.S. 5,738,855, col. 10, lines 30-33, which states that "[t]he Vi-rEPA was made as described in U.S. Pat. No. 5,204,098, issued Apr. 20, 1993. U.S. Pat. No. 5,204,098 describes polysaccharide-protein conjugates using SPDP as a linker). ADH is just one of a list of linkers mentioned in claim 14 of Szu et al U.S. Patent No. 5,738,855, but is not exemplified in the patent. Furthermore, Example 7 in column 15 of Szu et al U.S. 5,738,855 concerns immunizing humans with either Vi alone or a modified pectin-carrier conjugate, not with a *S. typhi* Vi polysaccharide-carrier conjugate wherein the Vi polysaccharide is derived from *S. typhi*. Similarly, Claim 49 is directed to "A method of actively immunizing a human against typhoid fever comprising: administering in vivo a sufficient amount of an O-acetylated plant, fruit or synthetic saccharide linked to a carrier, said amount is sufficient to elicit antibody that binds to Vi of *Salmonella typhi*" (emphasis added). There is no mention in Table 2, Example 7, claim 49 or anywhere else in Szu et al. 5,738,855 of immunizing with a Vi polysaccharide derived from *S. typhi* linked to *r*EPA via an adipic acid dehydrazide linker nor is there any teaching or suggestion to that effect. Furthermore, the O-acetylated pectin antigen of Szu et al. 5,738,855 differs from Vi derived from *S. typhi* by lacking the N-acetyl group.

In addition, Applicants also respectfully submit that the results described in the application were unexpected. For example, there was a significantly increased level of anti-Vi antibodies present at 6 months post-inoculation in 2- to 4-year olds for $rEPA_{II}$, as compared to the levels induced by $rEPA_I$. The $rEPA_{II}$ conjugate resulted in greater than 90% protection against typhoid fever in the 2- to 5-year old age group that was studied in the phase III clinical trial. The level of protection in 6- to 14-year olds and adults would be at least that of the 2- to 5-year olds, since older children and adults are usually better responders to vaccines than 2- to 4- (or 2- to 5-) year olds. A greater than 90% response rate is significant, since most vaccines (e.g., three or four cholera vaccines and the licensed typhoid vaccine) are only about 60% to 70% protective. Moreover, the Vi-$rEPA_{II}$ conjugate vaccine was more effective than Vi-polysaccharide and the Vi-$rEPA_I$ conjugate (i.e., *S. typhi* Vi polysaccharide linked to rEPA with a SPDP linker) in adult humans and was more effective than the Vi-$rEPA_I$ conjugate in all age groups. These results, especially the high levels of antibodies in 2- to 4-year olds 6 months after incubation, are significant. Such results are unexpected to one of ordinary skill in the art and are compelling evidence of non-obviousness.

Applicants respectfully submit that in view of the above amendments and remarks, the rejection of the claims under 35 U.S.C. §102(e) in view of the Szu et al (October 17, 1994) reference be reconsidered and withdrawn.

Miscellaneous

Fattom et al (1992, submitted in Applicant's PTO-1449) is being cited by the Examiner for showing the abbreviation "ADH" to mean adipic acid dihydrazide.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. If a telephone interview would advance the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: August 6, 2002

By: _____
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of inducing, in a human, serum antibodies which protect against infection with *S. typhi*, comprising administering to said human, a composition comprising a molecular conjugate of the *S. typhi* Vi polysaccharide derived from *S. typhi* covalently bound through [a carboxylic] an adipic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A in a pharmaceutically acceptable carrier.

2. (Cancelled) [The method of claim 1 wherein the *S. typhi* Vi polysaccharide is covalently bound to the *r*EPA by means of an adipic acid dihydrazide linker.]

3. (Amended) The method of claim 1 [or 2] wherein said conjugate molecule is administered at a dose of about 3 micrograms to about 50 micrograms of *S. typhi* Vi polysaccharide.

4. The method of claim 3 wherein said conjugate molecule is administered at a dose of about 25 micrograms of Vi polysaccharide.

5. (Amended) The method of claim 1 [or 2] wherein the antibodies protect the human against infection by *S. typhi*.

6-11. (Cancelled)

12. (Amended) A method for vaccinating a human against *S. typhi* infection, comprising administering to the human an immunizing amount of a composition comprising a molecular conjugate of *S. typhi* Vi polysaccharide derived from *S. typhi* covalently bound through [a carboxylic] an adipic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A in a pharmaceutically acceptable carrier.

13. (Cancelled) [The method of claim 12 wherein the *S. typhi* Vi polysaccharide is covalently bound to the *Pseudomonas aeruginosa* recombinant exoprotein A by means of an adipic acid dihydrazide linker.]

14. (Amended) A vaccine composition comprising an immunologically effective amount of a molecular conjugate of *S. typhi* Vi polysaccharide derived from *S. typhi* covalently bound through [a carboxylic] an adipic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A, in a pharmaceutically acceptable carrier.

15. (Cancelled) [The vaccine composition of claim 14 wherein the *S. typhi* Vi polysaccharide is covalently bound to the *Pseudomonas aeruginosa* recombinant exoprotein A by means of an adipic acid dihydrazide linker.]

16. (New) The method of claim 5 wherein the human is a 2 to 3 year old.

17. (New) The method of claim 5 wherein the human is a 4 to 5 year old.

18. (New) The method of claim 5 wherein the human is a 5 to 14 year old.

19. (New) The method of claim 5 wherein the human is an adult.

20. (New) The method of claim 12 wherein the human is a 2 to 3 year old.

21. (New) The method of claim 12 wherein the human is a 4 to 5 year old.

22. (New) The method of claim 12 wherein the human is a 5 to 14 year old.

23. (New) The method of claim 12 wherein the human is an adult.